R^3 is hydrogen, alkyl, halo, nitro, cyano, hydroxy, alkoxy;

an ester, a carbamate, or a pharmaceutically acceptable salt thereof.

51. (New) The compound of Claim 50, wherein R^1 is heteroalkyl.

52. (New) The compound of Claim 51, wherein R^1 is alkylsulfonylalkyl.

53. (New) The compound of Claim 52, wherein R^2 is alkyl.

54. (New) The compound of Claim 53, wherein A is $-(CH_2)-$.

55. (New) The compound of Claim 52, wherein R^2 is $NR^{13}R^{14}$ wherein R^{13} and R^{14} are hydrogen.

56. (New) The compound of Claim 55, wherein A is $-(CH_2)-$.

REMARKS

Claims 1-19 and 38-43 are pending in this application. Claims 1-4, 12, and 38 have been amended *inter alia* in view of the restriction requirement where X and Y are limited to CH. New Claims 50-56 have been added. Upon entry of this Amendment and Response Claims 1-19, 38-43, and 50-56 will be pending in this application with Claims 20-37 and 44-49 having been withdrawn from further consideration by the Examiner. New independent Claim 50 is directed to a compound of Formula I where among others B is aryl, or optionally substituted furyl, imidazolyl, pyridyl, thienyl, thiazolyl, benzothiazolyl or pyridazinyl; and R^1 is alkenyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, heteroalkyl or alkylcarbonylalkyl. Thus, some of the differences between compounds of Claim 1 and Claim 50 are (1) the aryl group in variable B of Claim 50 is optionally substituted aryl and (2) R^1 of Claim 50 excludes an alkyl group.

Attached hereto as Appendix A captioned "Version with Markings to show changes made" is a marked-up version of the changes made to the claims by the

current amendment. In addition, for the convenience of the Examiner, all claims now pending following entry of the present Amendment and Response are reproduced in Appendix B captioned "Pending Claims."

Rejection under 35 U.S.C. §112

The Examiner has maintained rejection of Claims 1-19 and 38-43 under 35 U.S.C. §112, first paragraph. In particular, the Office Action states "...the description of prodrug...is broad and it does enable [sic] one skilled in the art to determine how the prodrug is converted to active compounds, by what mechanisms...what in vivo enzymes are likely involved in cleaving the protected group, etc. All these factors are uncertain and require one skilled in the art to spend undue amount of time to practice the invention."

Claims of the present application are directed to compounds and compositions. There is no requirement to specifically provide how a prodrug is converted to an active compound. Moreover, one skilled in the art is well aware of typical mechanisms that are involved in converting a prodrug to its active compound. For example, it is well known that esters, carbamates, and amides are hydrolyzed by enzymes such as hydrolases, lipases, and esterases, etc. to generate the corresponding hydroxides and amines, etc. However, in order to expedite the prosecution of this application, Claim 1 has been amended by deleting the term "prodrug" and adding the terms "an ester" and "a carbamate". Support for such amendment can be found, for example, on page 9, lines 10-19.

The Office Action states the variable "R" in Claim 1 should be "R_2" in the definition of A.

The subscript "2" in the definition of A as being "R_2" represents the number of "R" substituents that are present on the carbon atom. Therefore, the variable "R" in Claim 1 in the definition of A is correct.

As suggested by in the Office Action, variable X and Y have been limited to CH due to the restriction requirement. In particular, Formula I has been redrawn by

deleting variables X and Y and replacing them with CH groups. In addition, in view of the new structure for Formula I, Claims 2 and 38 have been amended by deleting variables X and Y.

Rejection under 35 U.S.C. §102

A number of rejections were set forth under 35 U.S.C. §102(b) as allegedly being anticipated by the cited references. It is well established that claims are anticipated if, and only if, each and every element as set forth in the claim is found in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051 (Fed. Cir. 1989). As discussed in detail below, none of the cited references discloses every element of the present invention.

The Barton Reference

The Examiner has maintained rejection of Claims 1-5 under 35 U.S.C. §102(b) as allegedly being anticipated by Barton et al. (J. Am. Chem. Soc. 1993). In particular, the Office Action states that the term alkyl "should be given the broadest interpretation that includes fluorine substituted alkyl."

The term "alkyl" is defined on page 3, lines 17-19, as being "a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms...." (emphasis added). Moreover, the standard definition for alkyl in the art is having a generic formula C_nH_{2n+1}. (See exhibit A, page 34 of *Hawley's Condensed Chemical Dictionary*, 13th Ed., Lewis, Sr., John Wiley & Sons, Inc., New York, NY, 1997). Furthermore, halogen substituted alkyl groups are separately defined in the present application as "haloalkyl." See page 5, lines 7-9.

Therefore, the definition of "alkyl" can not include a trifluoromethyl group. Accordingly, the 35 U.S.C. §102(b) rejection of Claims based on the Barton reference is improper and should be withdrawn.

The Okada Reference

Claims 1-5 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by the Okada reference. In particular, the Office Action states that the pyrimidine ring in the compound discussed in the Okada reference corresponds to the variable R^1 of the present invention.

Even if *arguendo* this assertion is correct, it is submitted that the compounds discussed in the Okada reference are different from compounds claimed in the present invention. For example, the variable R^1 of Formula I of the present invention is limited to alkyl, alkenyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, heteroalkyl, and alkylcarbonylalkyl. As defined on page 6, lines 9-11, the term "heteroaralkyl" refers to a radical $-R^aR^b$ where R^a is an alkylene group and R^b is a heteroaryl group. Thus, when R^1 includes a pyrimidine ring (a heteroaryl group), it must attached to the nitrogen atom by an alkylene linker.

In contrast, if the pyrimidine ring of the compound discussed in the Okada reference corresponds to R^1, the Okada reference compound has the pyrimidine ring attached directly to the nitrogen atom, i.e., without an alkylene linker. Thus, it is clear that the compound discussed in the Okada reference is different from the compounds of the present invention. Accordingly, the 35 U.S.C. §102(b) rejection of Claims based on the Okada reference is improper and should be withdrawn.

The Billman Reference

Claims 1-5 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Billman et al. (J. Org. Chem., 1962) (the "Billman reference").

Compound V of the Billman reference that is referred to in the Office Action has an amino moiety that is substituted with an ethyl group and a benzyl group, which corresponds to groups R^1 and –A–B, respectively, of Formula I of the present invention. Specifically, the phenyl ring of the benzyl group of Compound V in the Billman reference corresponds to the variable "B" of Formula I of the present invention.

As amended, the moiety B is defined as substituted aryl, optionally substituted furyl, imidazolyl, pyridyl, thienyl, thiazolyl, benzothiazolyl or pyridazinyl. Thus, the aryl group is a substituted aryl group. In contrast, the phenyl group of

Compound V in the Billman reference is unsubstituted. Accordingly, the 35 U.S.C. §102(b) rejection of Claims based on the Billman reference is improper and should be withdrawn.

As for new Claim 50, the nitrogen atom in Compound V of the Billman reference comprises an ethyl group (i.e., an alkyl group). New Claim 50 specifically excludes R^1 as being an alkyl group.

The Katritzky Reference

Claims 1-5 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Katritzky et al. (Synthetic Communications, 1993) (the "Katritzky reference").

Compound 5 of the Katritzky reference that is referred to in the Office Action has an amino moiety that is substituted with a butyl group and a 3-phenylpropyl group, which corresponds to groups R^1 and –A–B, respectively, of Formula I of the present invention. Specifically, the phenyl ring of the 3-phenylpropyl group of Compound 5 in the Katritzky reference corresponds to the variable "B" of Formula I of the present invention. Similar to Compound V of the Billman reference, the phenyl ring of Compound 5 of the Katritzky reference is unsubstituted.

As stated above in the discussion regarding the Billman reference, the aryl group of the variable "B" of the present invention is a substituted aryl group. Therefore, the 35 U.S.C. §102(b) rejection of Claims based on the Katritzky reference is improper and should be withdrawn.

As for new Claim 50, the nitrogen atom in Compound 5 of the Katritzky reference comprises a butyl group (i.e., an alkyl group). New Claim 50 specifically excludes R^1 as being an alkyl group.

Rejection under 35 U.S.C. §103

Claims 1-5, 12, and 13 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Dinsmore et al. (Bioorganic and Medicinal Chemistry, 1999) (the "Dinsmore reference"). The Office Action states Compound 8a of the Dinsmore

reference differs from the compounds of the present invention "only in the nature of the substituent on the nitrogen atom (R is H in reference and R1 is alkyl in the instant invention)." The Office Action then states "the reference teaches the equivalence of H and alkyl in the definition of R.... Thus, one of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole."

It is submitted that the difference between compounds of the present invention and Compound 8a of the Dinsmore reference is more than R being H in the reference and R^1 is alkyl in the nature of the substituent on the nitrogen atom. The other substituent on the nitrogen atom is also different. Compound 8a has a 4-cyanophenyl substituted imidazolylmethyl group on the nitrogen atom. In contrast, when A is methylene and B is optionally substituted imidazolyl group in compounds of the present invention, the substituent on the imidazolyl moiety (i.e., a heteroaryl moiety) are limited to those defined on page 5, line 24, to page 6, line 3, including phenyl and phenyl alkyl listed on page 5, line 28. Specifically, the cyano-substituted benzyl group that is present in Compound 8a of the Dinsmore reference is not within the scope of the variable B in Formula I of the present invention. Therefore, the difference between Compound 8a of the Dinsmore reference and compounds of the present invention is more than simply the nature of the R^1 substituent on the nitrogen atom.

Furthermore, the Examiner's assertion, pointing to compounds 5b and 9 of Table 3, that the Dinsmore "reference teaches the equivalence of H and alkyl in the definition of R..." is inaccurate and contrary to the teaching of the Dinsmore reference. The variable X in Compounds 5b and 9 of the Dinsmore reference is O and S, respectively. In contrast, the variable in Applicants" invention that corresponds to X in Compounds 5b and 9 is SO_2. There is no data in Table 3 showing that H and alkyl are equivalent when X is SO_2; data is provided for only one compound (8a) where X is SO_2 and R=H and there is no corresponding compound where X is SO_2 and R=alkyl in Table 3. Therefore, Dinsmore's data in Table 3 does not teach that H and alkyl are equivalent in the context of Applicant's invention.

Moreover, in contrast to the assertion stated the Office Action, it is submitted that the Dinsmore reference actually teaches away from replacing hydrogen with an alkyl group in the nitrogen atom when X is SO_2. For example, the Dinsmore reference states "Also unexpected was that N-alkylation (R^2) with a hydrophobic group...did not cause the desired effect in the diarylsulfones." See page 3303, last paragraph. Table 4 of the Dinsmore reference shows that replacing R^2 (corresponding to Applicants' R^1) on the nitrogen atom from hydrogen with a hydrophobic group, i.e., CH_2–c-Pr, results in an almost 20 fold decrease in FTase inhibition, i.e., from 0.45 nM to 8 nM, respectively. Therefore, when X is SO_2, the Dinsmore reference discourages one skilled in the art from replacing hydrogen on the nitrogen atom with a hydrophobic group, such as an alkyl group, and teaches away from making this substitution.

In addition, as stated above, it is submitted that the compounds discussed in the Dinsmore reference are structurally different from the compounds of the present invention. For example, the imidazolyl moiety of Compound 8a of the Dinsmore reference is substituted with a 4-cyanobenzyl group. In contrast, the definition of heteroaryl on page 5, line 21, to page 6, line 8, shows that compounds of the present invention do not include such a substituent on the imidazolyl moiety.

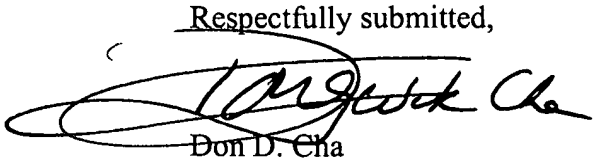
Accordingly, the 35 U.S.C. §103(a) rejection based on the Dinsmore reference is improper and should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the

Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 303-571-4000.

Respectfully submitted,



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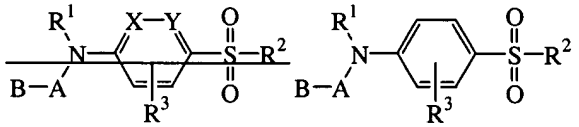
APPENDIX A
VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 1-4, 12, and 38 have been amended as follows:

1. (Amended Herein) A compound of the formula (I):



Formula I

wherein:

A is $-(CR_2)_n-$ where n is 1, 2 or 3 and **each** R is independently hydrogen or alkyl;

B is **substituted** aryl~~,~~ **or optionally substituted heteroaryl, wherein heteroary is** furyl, imidazolyl, pyridyl, thienyl, thiazolyl, benzothiazolyl or pyridazinyl;

~~**X and Y are, independently, CH or nitrogen;**~~

R^1 is alkyl, alkenyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, heteroalkyl or alkylcarbonylalkyl;

R^2 is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, or $NR^{13}R^{14}$ wherein:

R^{13} is hydrogen or alkyl;

R^{14} is hydrogen, alkyl, aklenyl, acyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, or aminoalkyl;

R^3 is hydrogen, alkyl, halo, nitro, cyano, hydroxy, alkoxy;~~**or prodrug, individual isomers, mixtures of isomers**~~ **an ester, a carbamate,** or **a** pharmaceutically acceptable salt thereof.

2. (Amended Herein) The compound of Claim 1, wherein~~:~~

R^3 is hydrogen~~; and~~

~~X and Y are both CH~~.

3. (Amended Herein) The compound of Claim 2 wherein B is **substituted** aryl.

4. (Amended Herein) The compound of Claim 3 wherein B is ~~optionally~~ substituted phenyl.

12. (Amended Herein) The compound of Claim 2 wherein B is **optionally substituted** heteroaryl**, wherein heteroaryl is furyl, imidazolyl, pyridyl, thienyl, thiazolyl, benzothiazolyl or pyridazinyl**.

38. (Amended Herein) The compound of Claim 1 wherein:

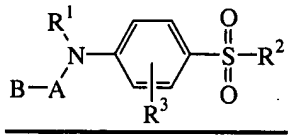
R^1 is alkylsulfonylalkyl; **and**

B is **substituted** aryl~~; and~~

~~X and Y are CH~~.

New Claims 50-56 have been added as follows.

50. (New) A compound of the formula:



wherein:

A is $-(CR_2)_n-$ where n is 1, 2 or 3 and each R is independently hydrogen or alkyl;

B is aryl or optionally substituted heteroaryl, wherein heteroaryl is furyl, imidazolyl, pyridyl, thienyl, thiazolyl, benzothiazolyl or pyridazinyl;

R^1 is alkenyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, heteroalkyl or alkylcarbonylalkyl;

R^2 is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, or $NR^{13}R^{14}$ wherein:

R^{13} is hydrogen or alkyl;

R^{14} is hydrogen, alkyl, aklenyl, acyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, or aminoalkyl;

R^3 is hydrogen, alkyl, halo, nitro, cyano, hydroxy, alkoxy;

an ester, a carbamate, or a pharmaceutically acceptable salt thereof.

51. (New) The compound of Claim 50, wherein R^1 is heteroalkyl.

52. (New) The compound of Claim 51, wherein R^1 is alkylsulfonylalkyl.

53. (New) The compound of Claim 52, wherein R^2 is alkyl.

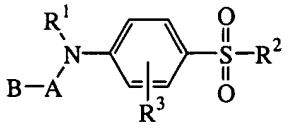
54. (New) The compound of Claim 53, wherein A is $-(CH_2)-$.

55. (New) The compound of Claim 52, wherein R^2 is $NR^{13}R^{14}$ wherein R^{13} and R^{14} are hydrogen.

56. (New) The compound of Claim 55, wherein A is $-(CH_2)-$.

APPENDIX B
PENDING CLAIMS

1. (Amended Herein) A compound of the formula (I):



Formula I

wherein:

A is $-(CR_2)_n-$ where n is 1, 2 or 3 and each R is independently hydrogen or alkyl;

B is substituted aryl or optionally substituted heteroaryl, wherein heteroary is furyl, imidazolyl, pyridyl, thienyl, thiazolyl, benzothiazolyl or pyridazinyl;

R^1 is alkyl, alkenyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, heteroalkyl or alkylcarbonylalkyl;

R^2 is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, or $NR^{13}R^{14}$ wherein:

R^{13} is hydrogen or alkyl;

R^{14} is hydrogen, alkyl, aklenyl, acyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, or aminoalkyl;

R^3 is hydrogen, alkyl, halo, nitro, cyano, hydroxy, alkoxy;

an ester, a carbamate, or a pharmaceutically acceptable salt thereof.

2. (Amended Herein) The compound of Claim 1, wherein R^3 is hydrogen.

3. (Amended Herein) The compound of Claim 2 wherein B is substituted aryl.

4. (Amended Herein) The compound of Claim 3 wherein B is substituted phenyl.

5. The compound of Claim 4 wherein R1 is alkyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl or heteroalkyl.

6. The compound of Claim 5 wherein R1 is heteroalkyl.

7. The compound of Claim 6 wherein R1 is alkylsulfonylalkyl.

8. The compound of Claim 7 wherein R2 is alkyl.

9. he compound of Claim 8 wherein A is –(CH2)–.

10. The compound of Claim 7 wherein R2 is NR13R14 wherein R13 and R14 are hydrogen.

11. The compound of Claim 10 wherein A is –(CH2)–.

12. (Amended Herein) The compound of Claim 2 wherein B is optionally substituted heteroaryl, wherein heteroaryl is furyl, imidazolyl, pyridyl, thienyl, thiazolyl, benzothiazolyl or pyridazinyl.

13. The compound of Claim 12 wherein R^1 is alkyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl or heteroalkyl.

14. The compound of Claim 13 wherein R^1 is heteroalkyl.

15. The compound of Claim 14 wherein R^1 alkylsulfonylalkyl.

16. The compound of Claim 15 wherein R^2 is alkyl.

17. The compound of Claim 16 wherein A is $-(CH_2)-$.

18. The compound of Claim 15 wherein R^2 is $NR^{13}R^{14}$ wherein R^{13} and R^{14} are hydrogen.

19. The compound of Claim 18 wherein A is $-(CH_2)-$.

38. (Amended Herein) The compound of Claim 1 wherein:

R^1 is alkylsulfonylalkyl; and

B is substituted aryl.

39. The compound of Claim 38, wherein R2 is alkyl.

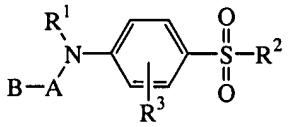
40. The compound of Claim 39, wherein A is –(CH2)–.

41. The compound of Claim 38, wherein R2 is NH2.

42. The compound of Claim 41, wherein A is –(CH2)–.

43. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable excipient.

50. (New) A compound of the formula:



wherein:

A is $-(CR_2)_n-$ where n is 1, 2 or 3 and each R is independently hydrogen or alkyl;

B is aryl or optionally substituted heteroaryl, wherein heteroaryl is furyl, imidazolyl, pyridyl, thienyl, thiazolyl, benzothiazolyl or pyridazinyl;

R^1 is alkenyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, heteroalkyl or alkylcarbonylalkyl;

R^2 is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, or $NR^{13}R^{14}$ wherein:

R^{13} is hydrogen or alkyl;

R^{14} is hydrogen, alkyl, aklenyl, acyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, or aminoalkyl;

R^3 is hydrogen, alkyl, halo, nitro, cyano, hydroxy, alkoxy;

an ester, a carbamate, or a pharmaceutically acceptable salt thereof.

51. (New) The compound of Claim 50, wherein R^1 is heteroalkyl.

52. (New) The compound of Claim 51, wherein R^1 is alkylsulfonylalkyl.

53. (New) The compound of Claim 52, wherein R^2 is alkyl.

54. (New) The compound of Claim 53, wherein A is $-(CH_2)-$.

55. (New) The compound of Claim 52, wherein R^2 is $NR^{13}R^{14}$ wherein R^{13} and R^{14} are hydrogen.

56. (New) The compound of Claim 55, wherein A is $-(CH_2)-$.